Sipuleucel-T Followed by Indoximod or Placebo in Metastatic Castration Resistant Prostate Cancer

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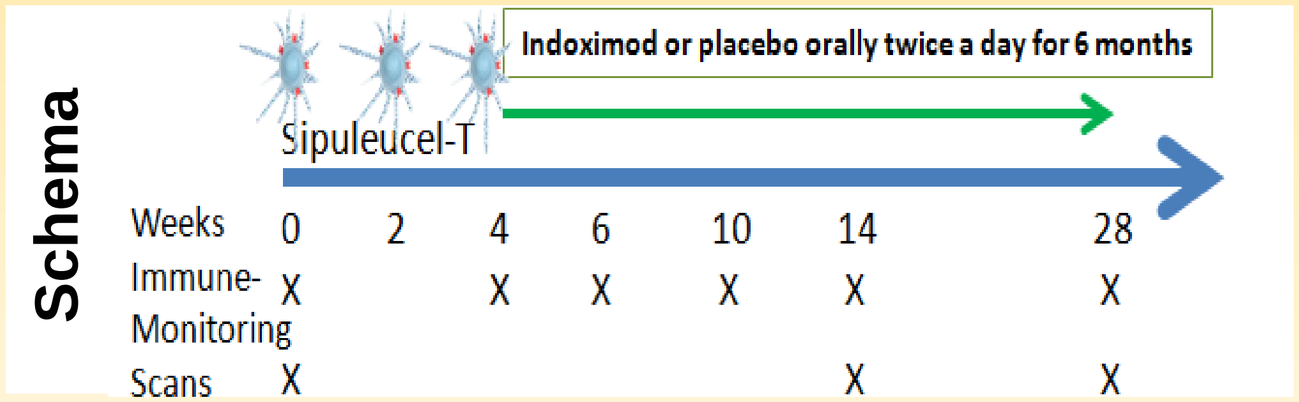
Introduction

- Tumor mediated immune-suppression by activation of inhibitory regulatory T cells poses a long term challenge for vaccine development[1-3]
- While sipuleucel-T (sip-T) likely circumvents this anergy by ex-vivo sensitization, immune response to sip-T could still be limited by tumor mediated immune-suppression.
- Indoleamine 2,3-dioxygenase (IDO) is a key immune-modulatory enzyme that degrades tryptophan and promotes peripheral immune tolerance by T cell inhibition and conversion of naïve T cells to Tregs.[4,5]
- Indoximod (1MT) is a broad inhibitor of the IDO Pathway and functions as a check point inhibitor by interfering with this key Pathway in tumor tolerance[6]

Hypothesis

- Inhibition of Tregs by indoximod will permit enhanced immune response to sipuleucel-T and lead to improved clinical outcomes



Study Timeline:

Methods: Phase II RDBCT Clinical Trial

Subjects: N=50, mCRPC with planned sip-T therapy; no opiate use for cancer pain, ECOG 0-1, not immune-suppressed, no auto-immune disease

Treatment: Oral indoximod or placebo post last sip-T infusion for 24 weeks unless disease progression or unacceptable toxicity

Monitoring

Primary objective:
- Augmentation of immune response to PA2024 at week 14 of therapy

Secondary objectives:
- Safety, PK
- Efficacy – OS, PFS, RR, CTC
- Quality of life

Immune endpoints:
- Tregs, NK cells, T cell subsets, MDSC, Macrophages in blood measured by 8 color flow cytometry
- Immune response to PA2024 - Ellispot, ELISA assays, CD54 upregulation
- Ratio of Kynurenine to Tryptophan for IDO inhibition
- Optional paired biopsy (pre-treatment and week 14) to assess immune response in tissue with IHC

Translation

- Proof of principle study to assess immune augmentation of vaccine by IDO pathway inhibition
- Could offer a well tolerated and effective option (to be tested in larger studies)

References:
1. Nat Rev Cancer. 2007;7(11):880-7, 2. Vaccine. 2007;25 Suppl 2:B72-88 3. Eur J Cancer. 2009;45(8):1424-31.
4. J Clin Invest. 2011;121(4):1361-72., 5. Oncogene. 2008;27(28):3889-900
6. Oncoimmunology. 2012 Dec 1;1(9):1460-1468.